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| 10/768,193 | 02/02/2004 | Katsuhiko Yanagisawa | 040036 | 3691 |

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| ART UNIT | PAPER NUMBER |
|---|---|
| 1649 | |

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Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/768,193 | YANAGISAWA ET AL. | |
| | Examiner | Art Unit | |
| | Kimberly A. Ballard | 1649 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *17 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-31* is/are pending in the application.

4a) Of the above claim(s) *11-31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/29/04, 12/15/04*, 2/2/04, 8/16/05.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### *Election/Restrictions*

Applicant's election without traverse of Group I, claims 1-10, drawn to an antibody that recognizes GM1 ganglioside-bound amyloid β-protein, in the reply filed on 17 May 2006 is acknowledged.

Claims 11-31 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 17 May 2006.

Claims **1-10** are under examination in the instant office action.

### *Priority*

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

### *Sequence Requirements*

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). This application fails to comply with the requirements of 37 C.F.R. §§ 1.821-1.825. Figures 1 and 2 contain sequences that are encompassed by the sequences rules and require sequence identifiers (SEQ ID numbers). It should be noted that when a sequence is presented in a drawing, regardless of the format or the

manner of presentation of that sequence in the drawing, the sequence must still be included in the Sequence Listing and the sequence identifier ("SEQ ID NO: X") must be used, either in the drawing or in the Brief Description of the Drawings. See MPEP 2422.02. Applicant is required to either amend the Figures with the corresponding SEQ ID numbers or alternatively applicant may amend the Brief Description of the Figures (beginning at page 12 of the specification) with the corresponding SEQ ID numbers. Applicant is reminded to check the entire disclosure to ensure that the application is in sequence compliance.

### *Specification*

The disclosure is objected to because of the following informalities: There are several instances within the specification wherein the symbol of a filled square (e.g., ■), designating a particular group in the corresponding drawings (such as in Figures 4 and 6), is instead denoted as a "¦". See for example, page 12, line 17; page 14, line 11; page 43, line 3; and page 47, line 2. It is noted that this may not be a complete listing of such typographical errors and Applicant is reminded to check the entire disclosure for any additional such typographical errors.

Appropriate correction is required.

### *Claim Objections*

Claims 1-10 are objected to because of the following informalities: claims 1-6 recite the phrase "the amino acid sequence *resulted* from a partial alteration...", wherein

the word "resulted" is grammatically awkward. The word "resulting" is suggested for use in place of "resulted". Claims 7-10 are similarly objected to as they depend from claims 1 and 2. Appropriate correction is required.

***Claim Rejections - 35 USC § 112, first paragraph***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an antibody, humanized antibody, or antigen-binding portion thereof (e.g., Fab, Fab', F(ab'), scFv, or dsFv) which recognizes GM1 ganglioside-bound amyloid β-protein, wherein the antibody comprises a heavy chain variable region comprising three complementarity determining regions (CDRs), or wherein the antibody comprises a light chain variable region comprising three CDRs, or wherein the antibody comprises a full set of six CDRs, three from the VH domain and three from the VL domain, does not reasonably provide enablement for an antibody, humanized antibody or antigen-binding fragment thereof that do not contain a full set of 6 CDRs from the VH and the VL domains (3 from each) or comprise VH or VL regions consisting of amino acid sequences resulting from partial alterations of the sequences (e.g., SEQ ID NOS: 1-8). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and, (8) the breadth of the claims. *In re Wands*, 8 USPQ2d, 1400 (CAFC 1988).

Claims 1-10 are broadly drawn to an antibody, or a humanized antibody or antigen-binding fragment thereof, which has an activity of recognizing GM1 ganglioside-bound amyloid β-protein and inhibiting the formation of amyloid fibrils, the antibody comprising at least one light chain CDR(s), or at least one heavy chain CDR(s), or a region of such CDRs or variable light or variable heavy chain regions consisting of an amino acid sequence resulting from a partial alteration of the amino acid sequence.

The specification discloses only antibodies 4396 and 4396C that contain both a VH and a VL chain and that specifically recognizes GM1 ganglioside-bound Aβ as described in Example 3 and Figure 5A. The specification fails to enable an antibody or antigen-binding fragment thereof that does not contain a full set of six CDRs (3 for each of the heavy and light chain variable regions) or that has partial alterations to the CDRs and is still capable of binding the recited antigen.

The specification defines "partial alteration of amino acid sequence" as an amino acid sequence that is altered by deletion or substitution of one to several amino acids constituting the amino acid sequence, or by addition or insertion of one to several amino acids, or by combination thereof (p. 14, line 22 – p. 15, line 1). The claims encompass

an antibody, humanized antibody or antigen-binding fragment thereof, which do not contain a full set of 6 CDRs or have partial alterations of the CDRs and thus are not commensurate in scope with the enablement provided in the specification. It is well established in the art that the formation of an intact antigen-binding site of all antibodies requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs or hypervariable regions, which provide the majority of the contact residues for the binding of the antibody to its target epitope (Paul, Fundamental Immunology, (textbook), 1993, pp. 292-295, under the heading "Fv Structure and Diversity in Three Dimensions"). The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity, which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites (Paul, page 293, first column, lines 3-8 and line 31 to column 2, line 9 and lines 27-30). Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al. (*Proc. Natl. Acad. Sci. USA,* 1982; 79: 1979-1983). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. It is unlikely that the antibody, humanized antibody,

and antigen-binding fragments thereof as defined by the claims, which may contain less than the full complement of CDRs from the heavy and light chain variable regions and may also contain alterations in the CDRs, have the required binding function. Applicants have provided insufficient evidence or nexus that would lead the skilled artisan to predict the ability of producing a humanized antibody or antigen-binding fragment thereof containing fewer than 3 CDRs for each heavy or light variable chain, or having alterations in the amino acid sequence of the CDRs, resulting in a humanized antibody or Fab fragment that retains the antigen specificity of the parental antibody. One of skill in the art would neither expect nor predict the appropriate functioning of the antibody as broadly as is claimed.

Therefore, in view of the lack of guidance in the specification and in view of the discussion above, one of skill in the art would be required to perform undue experimentation in order to practice the claimed invention as it pertains to an antibody, humanized antibody or antigen-binding fragment thereof. Undue experimentation would indeed be required to produce the invention commensurate with the scope of the claims from the written disclosure alone.

### *Claim Rejections - 35 USC § 112, second paragraph*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Section a) of claim 1 recites the phrase "the amino acid resulted from a partial alteration of SEQ ID NO: 1". The phrase is indefinite and ambiguous because it is unclear how "a first region" of the heavy chain variable region (i.e., CDR1 of the HC variable region) can consist of a single amino acid. It is noted that addition of the word "sequence" following "amino acid" would obviate this rejection.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-6 are rejected under 35 U.S.C. 102(b) as being anticipated by Yanagisawa et al. (1997) *FEBS Lett*ers, **420**: 43-46 (listed on Applicant's IDS filed 4/29/2004).

Yanagisawa et al. teach the monoclonal antibody 4396, which was raised against membrane fractions prepared from the cerebral cortices of subjects with abundant diffuse plaques (see pp. 43-44, sections 2.2-2.4), and which recognizes GM1 ganglioside-bound Aβ1-40 and Aβ1-42 (see p. 45, section 3.3). It is noted that the antibody 4396 is the same as disclosed in the instant specification (see for example p.

4, lines 23-25 of the specification; the instant specification also discloses the antibody 4396C which has the same variable region as 4396, p. 7, lines 8-10). Accordingly, the 4396 antibody disclosed by Yanagisawa et al. would inherently comprise the regions set forth in SEQ ID NOS: 1-6 (the heavy and light chain CDRs) and SEQ ID NOS: 7 and 8 (the heavy and light chain variable regions, respectively), and the antibody would inherently possess the ability to inhibit the formation of amyloid fibrils. Thus, the 4396 monoclonal antibody taught by Yanagisawa et al. anticipates the antibody of claims 1-6.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 7-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yanagisawa et al. (*FEBS Lett*ers, 1997; **420**: 43-46), in view of US Patent No. 5,530,101 to Queen et al., 25 June 1996 and Webber et al. (*Mol Immunol*, 1995; **32**(4): 249-258).

The claims are drawn to a humanized antibody that recognizes GM1 ganglioside-bound amyloid β-protein (GM1/Aβ) and inhibits the formation of amyloid fibrils. The claims are also drawn to an antibody Fab, Fab', F(ab'), scFv, or dsFv which recognizes GM1/Aβ.

The teachings of Yanagisawa et al. are discussed above. Briefly, Yanagisawa et al. teach the monoclonal antibody 4396, which recognizes GM1 ganglioside-bound Aβ1-40 and Aβ1-42 (see p. 45, section 3.3). Yanagisawa et al. also teach that the 4396 monoclonal antibody may be useful as a probe to gain insight into the initial molecular mechanism of Aβ deposition, including the generation of GM1 ganlioside-bound Aβ (GM1/Aβ), in the brains of patients with Alzheimer's disease (see p. 46, bottom of 1$^{st}$ column). However, Yanagisawa et al. do not teach humanized 4396 antibody or additional antibody binding forms, such as Fab, Fab', F(ab'), scFV or dsFV.

Queen et al. teach the preparation of humanized antibodies, wherein each humanized immunoglobulin chain comprises, in addition to CDRs, amino acids from the donor immunoglobulin framework, and an accepting human framework immunoglobulin (column 2, lines 35-59). Queen et al. also teach that immunoglobulins may exist in a variety of other forms, such as Fv, Fab, and $(Fab')_2$ (column 11, lines 25-28). Additionally, Queen discloses that humanized antibodies are substantially non-immunogenic in humans yet retain substantially the same affinity as the donor immunoglobulin to the antigen (see Abstract).

Webber et al. teach the preparation and characterization of disulfide-stabilized Fv fragments (dsFv) in comparison with their single-chain (scFv) analogs. Webber teaches that because of their small size, scFvs are useful as probes because they have superior tissue penetration and are cleared quickly from the circulation (p. 249, 2nd paragraph). However, scFvs have the drawback of being difficult to produce in large quantities. Webber teaches that a prepared dsFv molecule binds with the same affinity as IgG (see p. 255, Figure 6) and can be produced in much higher yields that the analogous scFv (see p. 257, 2nd paragraph). Further, Webber notes that dsFvs are significantly more resistant to denaturation by either heat or chaotropic agents (see p. 256, Figure 7).

It would have been obvious to one of skill in the art at the time the invention was filed to either modify the 4396 monoclonal antibody taught by Yanagisawa et al. to produce either humanized antibodies or binding fragments as taught by Queen et al., or to produce scFv or dsFv molecules as taught by Webber et al. One of skill in the art would be motivated to make such modifications because Yanagisawa teaches that the

4396 monoclonal could be used as a probe to study disease progression in the brains of patients with Alzheimer's disease, while Queen teaches that humanized antibodies are less immunogenic when administered to humans compared to the non-human monoclonal antibodies from which they are derived. Additionally, Webber teaches that dsFv molecules are valuable as probes because their small size allows them to effectively penetrate various tissues, the disulfide bounds makes dsFvs more stable and capable of being produced in greater quantities than scFv molecules, and dsFvs retain affinity for antigen equivalent to the parent IgG molecule. The skilled artisan would have a reasonable expectation that the humanized or dsFv 4396 antibody would still recognize GM1 ganglioside-bound Aβ because both Queen and Webber teach that modification of the parent immunoglobulin, either by humanizing the antibody or producing a dsFv molecule, does not affect the affinity of the molecule. In each case, the modified antibody (or antibody fragment) retains substantially the same affinity as the donor (parent) antibody. Thus, the combined teachings of the above references render obvious instant claims 7-10.

***Conclusion***

No claims are allowed.

***Advisory Information***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly A. Ballard whose telephone number is 571-272-4479. The examiner can normally be reached on M-F 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Kimberly Ballard, Ph.D.
Art Unit 1649
July 26, 2006

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